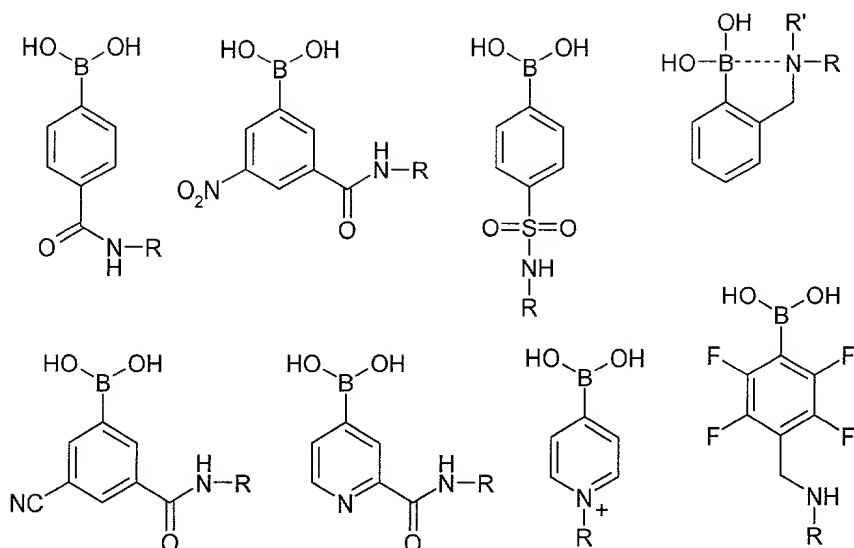


## CLAIMS

1. An insulin derivative comprising a glucose-sensing group.
2. The insulin derivative of claim 1, wherein the insulin derivative is a natural insulin or  
5 an insulin analogue.
3. The insulin derivative of claim 1, having a glucose affinity in the range of 0.01  $\mu$ M to 10 mM.
- 10 4. The insulin derivative of claim 1, wherein the glucose-sensing group is an aryl boronate group.
5. The insulin derivative of claim 4, wherein the aryl boronate group comprises an electron-withdrawing substituent.  
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6. The insulin derivative of claim 5, wherein the electron-withdrawing substituent is selected from the group consisting of sulfon, carboxy, nitro, cyano and fluoro.
7. The insulin derivative of claim 5, which has an amino group in proximity to the  
20 boronate moiety in the form of a 2-aminomethylarylboronate.
8. The insulin derivative of claim 7, which has an amino group within 2.0 Ångstrom from the boron atom.
- 25 9. The insulin derivative of claim 4, wherein the arylboronate group is selected among the following groups, wherein R designates the insulin moiety including a lipophilic substituent and an optional linker, and R' designates hydrogen, methyl, ethyl, propyl, isopropyl or benzyl:



10. The insulin derivative of claim 4, wherein the arylboronate group is attached to the insulin moiety via the  $\alpha$ -amino group of GlyA1 or PheB1, or via the  $\epsilon$ -amino group of a Lys residue at position B3, B28, B29 or B30 or a Orn residue, a Dap residue, a Dab residue, an Asp residue or a Glu residue at position B30.

11. The insulin derivative of claim 4, wherein the arylboronate group is attached to the insulin moiety via a linker.

12. The insulin derivative of claim 11, wherein the linker is selected from the group consisting of  $\gamma$ -glutamyl,  $\alpha$ -glutamyl,  $\beta$ -aspartyl,  $\alpha$ -aspartyl,  $\beta$ -alanine, piperazine and aniline.

13. The insulin derivative of claim 4, wherein the glucose sensing aryl boronate is a part of the amino acid residue in position B26 of the insulin moiety.

14. The insulin derivative of claim 1, wherein the glucose sensing group is a peptide or pseudopeptide, optionally comprising Asn, Trp, His, Asp, Arg or a boronate containing amino acid.

15. The insulin derivative of claim 14, wherein the glucose sensing peptide is comprised within the residues 26-30 of the B-chain, optionally extended beyond the C-terminal residue 30 of the B-chain.

16. The insulin derivative of claim 1, wherein the glucose-sensing group is built into a substituent capable of effecting the formation of high molecular aggregates.

17. The insulin derivative of claim 16, wherein the glucose-sensing group is an aryl boronate and the substituent causing aggregation is a lipophilic group.
18. The insulin derivative of claim 17, wherein the lipophilic group is a derivative of a bile acid selected from the group comprising lithocholic acid, hyocholic acid, hyodeoxycholic acid and chenodeoxycholic acid.
19. The insulin derivative of claim 18, wherein the lipophilic group is attached to the insulin moiety via a  $\gamma$ -glutamyl,  $\alpha$ -glutamyl,  $\beta$ -aspartyl,  $\alpha$ -aspartyl or  $\beta$ -alanine spacer.
20. The insulin derivative of claim 17, wherein the lipophilic group is a derivative of an  $\alpha,\omega$ -dicarboxylic acid having from 10 to 30 carbon atoms.
21. An insulin derivative comprising a monosaccharide, disaccharide, trisaccharide or a polyol group, capable of binding to an insulin derivative having a glucose-sensing group.
22. The insulin derivative of claim 1, further comprising a monosaccharide, disaccharide, trisaccharide or a polyol substitution.
23. The insulin derivative of claim 1, capable of forming water soluble, high molecular aggregates having a molecular weight > 150 kDa.
24. A water soluble, protracted, glucose dependent pharmaceutical composition comprising one or more of the insulin derivatives of claim 1.
25. A soluble, biphasic-acting insulin preparation comprising one or more of the insulin derivatives of claim 1, mixed with human insulin or an insulin with rapid onset of action, such as human insulin or des(B30) human insulin or Asp<sup>B28</sup> human insulin or Lys<sup>B28</sup>Pro<sup>B29</sup> human insulin or Gly<sup>A21</sup>,Lys<sup>B3</sup>,Ile<sup>B28</sup> human insulin, or Asp<sup>A21</sup>,Lys<sup>B3</sup>,Ile<sup>B28</sup> human insulin in ratios from 10:1 to 1:10.
26. A soluble insulin preparation characterized by having a rate of absorption from an injected depot, which rate of absorption increases as the glucose concentration in the tissue increases, and decreases as the glucose concentration decreases.
27. Crystalline preparations of one or more of the insulin derivatives of claim 1.

28. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the insulin derivative of claim 1.